New angiography method by proton magnetic resonance imaging

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Preamble.

The description of this angiography method placed herewith was presented to the Société Guerbet during a meeting organized at their registered office at 16-24 rue Jean Chaptal at Aulnay-sous-Bois on 14.03.02. A secret agreement binding the Société Guerbet and the laboratory representing the CNRS and the University of Bordeaux 2 was signed and is also placed herewith.

TITLE of the method:

C.S.A. Chemical Shift Angiography
(in French "Angiographie de Déplacement Chimique", ADC)

Introduction: principle of the method

This is the description of a new angiography method by proton magnetic resonance, based on the chemical shift of water protons in the presence of chemical shift agents (dysprosium, praseodymium, etc.). The existing methods are based on setting up a contrast resulting from changes in the relaxivity of water in the presence of contrast agents changing the relaxation rates of water in their immediate environment. The originality of the proposed method lies in the use of the chemical shift phenomenon in order to produce selective imaging of the compartment containing the reagent (vessels). This idea has never been presented in the literature and has never been utilized. This angiography principle may prove to be a method of choice for cell targeting and molecular imaging *in vivo*.

Experimental conditions:

Reagent used: dysprosium-DOTA (initial concentration 0.5M) made by the Société Guerbet corporation (16-24 rue Jean Chaptal in Aulnay-sous-Bois).

Phantom:

The phantom consists of a tube with a diameter of 5 mm containing the 2 mM dysprosium-DOTA aqueous solution inserted in a tube with a diameter of 20 mm containing distilled water. Dysprosium-DOTA under these conditions causes a shift of the resonance frequency of the water protons located in its close vicinity by about 80 Hz towards low values of the screen constants.

Animal:

Animal measurements are carried out on a male rat (Sprague-Dawley, of 150 g). The animal was anesthetized with chloral hydrate by intraperitoneal injection. The dysprosium solution was injected via an intravenous route as a bolus in order to obtain a blood concentration close to 2 mM.

Imaging: (equipment; sequence, procedure): the measurements were carried out on an imaging spectrometer Biospec 47/50 (Bruker Medical, Ettlingen, Germany). Transmission and reception of the signal were obtained with a Helmholtz antenna adapted to the head of the rat. The applied imaging sequence is of the 3D gradient echo type provided with a binomial pulse (1-3-3-1) having the effect of suppressing the signal of non-shifted water. It allows

selective imaging of the signal of the water having been shifted by the proximity of dysprosium.

The measurements concerning the phantom were obtained with the following parameters:

Repetition time: 33.8 ms, echo time: 5.2 ms, matrix: 128 x 128 x 16, viewing field: 6 cm x 3 cm x 3 cm.

On animals, the viewing field and the matrix were adapted, (viewing field: 4 cm x 4 cm x 4 cm, matrix: 128 x 128 x 32). The images were postprocessed (0 filling, Gaussian filter on the raw data) by means of the IGOR wavemetrics software.

Procedure:

Certain elements from the family of lanthanides are known for shifting the resonance frequency of protons of water molecules located in their close vicinity. The chemical shift reagent as DOTA chelate is administered intravenously. A 2D or 3D imaging sequence, selective in frequency, specifically imaging the shifted protons by the chemical shift agent is then applied. Within a short period following the injection, the chemical shift agent is only present in the vascular sector. The NMR image therefore produces a specific mapping of this sector. The experimental procedure therefore comprises:

An intravenous injection of the chemical shift agent in solution (bolus).

Production of a 2D or 3D rapid imaging sequence selective in frequency during the diffusion of the product in the vascular compartment.

Experimental results:

a) On the phantom: Figs. 1 and 2 respectively show the image of the phantom with and without suppression of the water signal.

b) On the animal: Fig. 3 shows an image of the rat head in the absence of suppression of the water signal. Fig. 4 shows the same image with suppression of the water signal and after injecting the dysprosium solution. The carotids then appear as a hypersignal.

The results obtained on the phantom clearly show the benefit of the CSA method for selectively mapping the compartment containing the dysprosium-DOTA solution. The results acquired *in vivo* on animals show the potential benefit of the method in the field of magnetic resonance angiography by MRI.

Specific advantages of the CSA method:

As compared with existing magnetic resonance angiography methods.

- Unlike the time-of-flight and phase contrast method, the CSA method is not based on the detection of the movement and therefore allows viewing of immobile blood or moving with a slow velocity. It does not require any *a priori* knowledge on the blood flow rate.

- Angiography methods in the presence of a contrast agent use the increase in relaxivity T1 (gadolinium complex) consecutive to injection of the contrast product. These contrast products generally have a concomitant action on T2 (decrease) inexorably leading to a decrease in the spatial resolution. The CSA method based on a different principle (chemical shift) should be able to limit this defect.

- The effect obtained with dysprosium-DOTA may be amplified by using reagents which cause a more significant chemical shift (praseodymium chelate). In this case, the CSA method may be contemplated on clinical imagers with lower static induction (1.5T). In the case when the shift is larger, the use which has been made possible, of sequences with smaller bandwidths may allow a significant increase in the signal-to-noise ratio.

- By allowing significant suppression or reduction of the signal from certain tissues (water), the method may prove to be of high interest for detecting low positive

contrasts. The latter would be masked by the signal from the surrounding tissues in the absence of suppression of the water signal. Potential applications in imaging targeted at the expression of genes and in molecular imaging seem to be important.

C.S.A.

Phantom images:

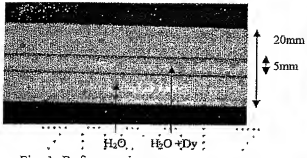

Fig. 1: Reference image

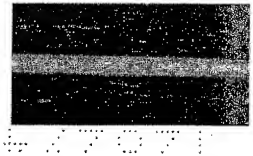

Fig. 2: With water signal suppression

Images of the rat head:

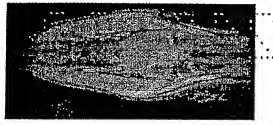

Fig. 3: Reference image

Fig. 4: With H_2O signal suppression and after injection of dysprosium

Secret agreement

Between Guerbet
15 rue des Vanesses 93420 Villepinte
(PO Box 50400 – 95943 – Roissy CdG)
represented by Claire Corot, Research Director
on the one hand

and the Centre National de la Recherche Scientifique
the registered office of which is at 3 rue Michel Ange 75794 Paris
represented by its General Director Geneviève Berger
which has delegated her signature to Jeanne Jordanov,
delegate from Aquitaine and Poitou-Charentes

hereafter CNRS

acting both in her name and in the name of and on behalf of the Unité Mixte de Recherches 5536, Magnetic resonance of biological systems, supervised by Prof. Paul Canioni,

hereafter the Laboratory

and Université Victor Segalen of Bordeaux 2
146 rue Léo Saignat – 33076 – Bordeaux
represented by .....
acting both in their name and in the name and on behalf of the laboratory on the other hand

whereas

Guerbet and the Laboratory which collaborate with other research teams within the framework of an incentive concerted action, designated as GENIMAG, now wish to examine whether another collaboration relating to contrast products for magnetic resonance angiography, may be started up together and for this the Laboratory has proposed to Guerbet that their work be explained in this field,

As a result, the parties will exchange during meetings or in writing, information which should remain confidential in order to ensure protection of the latter against untimely use or non-authorized disclosure to third parties.

The Parties commit themselves

- to only provide this information to their permanent members of Guerbet and of the Laboratory respectively, which will be subject to the provisions of the present secret agreement
- to take all the reasonable steps in order to prevent this personnel from disclosing to third parties, without written authorization of the Party which will have transmitted all or part of this information,
- to not filing a patent application or any other industrial property title including this information without written authorization from the other Party.
- to only use this information for examining the conditions of possible future collaboration in this field and not to use them with the purpose of direct or indirect exploitation without the written authorization of the other Party.

None of the present provisions should be interpreted as granting to Guerbet or to the Laboratory a licence and/or any privilege, on any ground whatsoever, on the use of the information. Any use of the information for an object other than the one indicated in the present agreement should therefore be subject to prior signature of a specific agreement.

This commitment does not relate to information which is or will be public domain information, that which is known to the party receiving it before it is passed onto them, that which would be developed independently by them nor that which an authorized third party would subsequently pass on to them.

The present secret agreement will concern information exchanged for one year from the date of March 14th 2002, the day of the first meeting of Guerbet and the Laboratory at Aulnay.

The provided confidentiality obligations should be observed by the parties for 20 years after March 14th 2002.

Any modification to the agreement will have to be reported in writing.

Drawn up with 4 copies

Guerbet	Centre National de la Recherche Scientifique	Université Bordeaux 2
date	date	date

14 Mars 2002

The Laboratory

date

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BAREME DE FRAIS ET HONORAIRES 2009
de notre Etude en matière de constat

Pour le temps passé en semaine, pendant les heures ouvrables (de 8h30 à 19h), à savoir : Déplacements aller/retour et temps sur place. En cas de photographies : 2 vacations aller/retour chez le photographe (dépôt et retrait), ou traitement et impression des photos numériques. En cas de film vidéo : transfert sur ordinateur, réalisation des gravures sur DVD, jaquettes, contrôles. Entretiens téléphoniques, rédaction, contrôle et mise en forme du procès-verbal.

Honoraires Hors Taxes, incluant le Procès-verbal :	**Euros**
Temps de l'Huissier de Justice, coût HT/heure :	280,00
Temps de collaborateur, coût HT/heure :	230,00
Temps de secrétariat, coût HT/heure :	73,00
Taxe de transport en vigueur, actuellement :	6,52
TVA à 19,60%	
Taxe fixe versée au Trésor Public en vigueur, actuellement :	9,15
A ajouter, le cas échéant :	
Coût HT unitaire par tirage authentifié de photographies :	1,80
Annexes authentifiées en noir et blanc, coût HT/unité :	0,75
Annexes authentifiées en couleurs, coût HT/unité :	0,95
Vidéo du film réalisé, par copie sur DVD, celle(s) conservée(s) à l'Etude + celle(s) remise(s) :	28,00
Diligences effectuées en urgence : Majoration de 10 % avec un minimum de :	105,00
Porteur en normal PARIS :	10,00
Porteur en urgence PARIS :	30,00

NOTA :

- Le temps varie en fonction de la durée de la vacation aller/retour, des constatations à établir sur place lors du rendez-vous, et du temps nécessaire ensuite pour la rédaction du procès-verbal.
- Le coût minimum d'un constat est de 230 Euros HT.
- La vidéo, utilisée pour les constats de grande ampleur, permet de réaliser des économies en photographies et en rédaction.
- Pour le temps passé en dehors des heures ouvrables (avant 8h30 et/ou après 19h), les taux horaires indiqués ci-dessus sont majorés de 50%. Pour le temps passé les samedi, dimanche ou jour férié, les taux horaires indiqués ci-dessus sont majorés de 100%.
- Le procès-verbal de constat sera adressé après réception du paiement soit d'une provision préalable, soit de la facture définitive, conformément aux articles 21 et 22 du décret n° 96-1080 du 12 décembre 1996.

(Nous consulter pour tous les autres types de constat : Constats sur ordonnance, sur informatique ou sur l'Internet, constat de dépôt de créations, mises sous scellés, jeux-concours, affaires complexes, etc ...)

Inscrire « Bon pour accord », la date, et apposer votre signature
(pour une société : son cachet et la signature d'une personne habilitée)

Bon pour accord 07/10/09